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| 10/684,539                                                                   | 10/14/2003  | Janet A. Warrington  | 9900.1005           | 5589             |
| 20601                                                                        | 7590        | 09/25/2006           | EXAMINER            |                  |
| SPECKMAN LAW GROUP PLLC<br>1201 THIRD AVENUE, SUITE 330<br>SEATTLE, WA 98101 |             |                      | BAUSCH, SARA E L    |                  |
|                                                                              |             |                      | ART UNIT            | PAPER NUMBER     |

1634

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/684,539

Applicant(s)

WARRINGTON ET AL.

Examiner

Sarae Bausch

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 13, 15 and 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 14 is/are rejected.
- 7) ☒ Claim(s) 1 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                                                |                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                           | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>04/04</u> . | 6) <input type="checkbox"/> Other: _____                                                |

### DETAILED ACTION

1. This action is in response to applicants correspondence mailed 08/03/2006.

#### *Election/Restrictions*

2. Applicant's election without traverse of group I, linking claims 1-10 and claims 11-14 in the reply filed on 08/03/2006 is acknowledged.
3. Claims 13, 15-16 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/03/2006.
4. A telephone election to clarify the restriction requirement mailed 03/03/2006 was made on 09/05/2006. In the restriction requirement, applicant was request to pick a specific gene or combinations of genes. During a telephone conversation with Janet Sleuth on 09/05/2006 a provisional election was made with traverse to prosecute the invention of alpha-1-antitrypsin, claims 12 and 14. Affirmation of this election must be made by applicant in replying to this Office action. Claim 13 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

#### *Specification*

5. The disclosure is objected to because of the following informalities:
  - (a). The specification refers to table 1 and table 2 on page 21, lines 24-25 and 31, however there are no tables present in the specification.
  - (b). The specification cites Visco however the specification does not provide a proper citation.

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(c). The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, see page 27, line 22 and page 28, line 31.

Appropriate correction is required.

### ***Claim Objections***

6. Claim 1-12 and 14 are objected to because of the following informalities: Claim 1 contains spelling errors that are a result of spacing errors, for example line 4 has the phrase “w ith”, “d iffere ntial”. Claim 1 recites “SUI” in line 4 of the claim. SUI is not defined in the specification nor defined in the claims. Appropriate correction is required.
7. Claim 14 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 12. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### ***Claim Rejections - 35 USC § 112- 2<sup>nd</sup> Paragraph***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
  9. Claims 1-12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
- (a). Claims 1-12 and 14 are indefinite. Claims 1-12 and 14 are drawn to a

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method of diagnosing stress urinary incontinence or predisposition to stress urinary incontinence in a premenopausal subject. The final process step is comparing the obtained results with a predetermined indicator of differential expression of said genes in SUI subjects relative to normal continent subjects. Accordingly the claims are ambiguous because the preamble recites a limitation that is not recited in any of the process steps and it is unclear the metes and bounds of the claims. Applicant should amend the claims to indicate how the step of comparing the obtained results with a predetermined indicator of differential expression of said gene is SUI subjects relative to normal continent subjects results in predicting the response of a human subject to a treatment designed to assist smoking cessation.

(b). Claims 2 and 3 are indefinite. Claim 2 recites “proliferative (estrogen only)” and claim 3 recites “secretory (estrogen + progesterone)”, which renders the claim indefinite because it is unclear whether the limitations in the parenthesis are part of the claimed invention.

***Claim Rejections - 35 USC § 112-Written Description***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-12 and 14 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at [www.uspto.gov](http://www.uspto.gov)).

The rejected claims are broadly drawn to methods for diagnosing stress urinary incontinence by analyzing gene expression in a pelvic supporting tissue. The rejection claims require comparing the results of gene expression in a pelvic supporting tissue with a predetermined indicator. The rejected claims further require the alpha 1 antitrypsin probe on an array.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to diagnosing stress urinary incontinence by analyzing any reproductive hormone-modulated gene expression and comparing this gene expression to a predetermined indicator. The specification does not define the terms “gene”, “reproductive hormone-modulated gene expression” “predetermined indicator” or “alpha 1 antitrypsin”. The specification asserts that a predetermined indicator may be empirically determined differential values obtained by parallel measurements of SUI pelvic supporting tissues and matched tissues of normal controls or alternatively may be a gene expression profile of a pelvic supporting tissue of the same subject determined at the time prior to the appearance of symptoms of pelvic floor dysfunction (see page 3, lines 31-35). The specification does define “hormone dependent gene expression” which refers to gene expression that is modulated in the presence of a hormone on page 20, line 33-35 but does not define hormone modulated gene expression. Thus the rejected claims encompass analysis of any portion of any variant of any gene from any organism, which may include gene sequences very different

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from the disclosed genes listed in figure 3, including sequences containing any polymorphisms (e.g. any insertion, deletion, or repeat at any location within the gene) and mutations not taught by the instant specification and not yet known in the art and further comparing the analysis of the gene expression to an indicator gene, which encompasses analysis of gene expression of the same gene in a normal subject, gene expression of the same gene in a subject prior to appearance of pelvic floor dysfunction, or some other gene expression level.

In analyzing whether the written description requirement is met for genus claims for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Nucleic acids of such a large genus as encompassed by the rejected claims have not been taught by the specification. The specification of the instant application does not disclose any nucleic acid sequence by their complete structure. The specification lists gene names, see figure 3, however the specification does not disclose the nucleic acid or amino acid structure for the gene names. Furthermore the specification does not define "alpha 1 antitrypsin" or provide the nucleic acid structure for "alpha 1 antitrypsin". The gene name "alpha 1 antitrypsin" encompasses a variety of known variants as well as yet to be discovered polymorphism variants and alternatively splice variants (see gene card, page 7). In addition, there are currently eight known species of alpha 1 antitrypsin and 87 different variants of human alpha 1 antitrypsin (see gene card, page 7). The specification does not provide any disclosure as to the association of each of these genes to diagnosis of stress urinary incontinence.

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Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the gene name of alpha 1 antitrypsin. The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of stress induced urinary incontinence based on analysis of gene expression of the non-disclosed gene.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, one of skill in the art cannot envision the detailed chemical structure of the encompassed polynucleotides (i.e. any alpha 1 antitrypsin genes of which is indicative of stress urinary incontinence, any predetermine indicator), regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that genes and predetermined indicators are part of the claimed invention. The nucleic acid itself is required.

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In conclusion, the limited information provided regarding the association of any gene expression level and predetermined indicator, specifically alpha 1 antitrypsin with stress urinary incontinence is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of methods comprising the analysis of any gene expression and predetermined indicator besides those particularly disclosed in the specification at the time the application was filed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

***Claim Rejections - 35 USC § 112-Enablement***

12. Claims 1-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims

The claims are drawn to a method of diagnosing stress urinary incontinence or predisposition to stress urinary incontinence (SUI) by analyzing reproductive hormone modulated gene expression in pelvic supporting tissue and comparing the results with a predetermined indicator of differential expression of genes in SUI subjects relative to normal continent subjects. The claims are further limited to tissues obtained during proliferative phase and secretory phase of the menstrual cycle. The claims are also limited to a predetermined indicator that comprises empirically determined differential gene expression values obtained by parallel measurements of SUI pelvic supporting tissues and matched tissues of normal controls as well as a gene expression profile of pelvic supporting tissue of the same subject determined at a time prior to the appearance of symptoms of pelvic floor dysfunction. The claims are further limited to analysis using a nucleic acid array with a probe for alpha 1 antitrypsin.

The rejected claims encompass analysis of any premenopausal subject, including human or non-human. The rejected claims encompass analysis of any gene expression, up or down regulated, in any pelvic supporting tissue and comparing the results with any predetermined indicator, which can encompass the same gene as detected in the sample, a different gene, or an enzyme.

The nature of the claims requires knowledge of a correlation between a gene and SUI. The claims require the knowledge of a correlation between differences in gene expression in a premenopausal subject with SUI and knowledge of a predetermined indicator that is associated with non-SUI subjects. The claims require the knowledge that

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differences in gene expression between the SUI subject and the predetermined indicator are an indication of SUI.

Guidance in the Specification and Working Examples

The specification asserts a method for the diagnosis of SUI by identifying reproductive hormone-dependent differential gene expression in pelvic supporting tissue of premenopausal subjects with SUI and subjects predisposed to SUI (see page 1, lines 18-22). The specification asserts that the pathophysiology of SUI is complex and not well understood (See page 2, line 9-10) that progress has been slow due to the complex extracellular matrix interactions that occur simultaneously and the difficulty of obtaining adequate tissue samples has restricted analysis to only a few enzymes at a time (See page 2, lines 33-35). The specification asserts that the method comprises using a nucleic acid array comprising one or more genes selected from the group consisting of genes that are up or down regulated during proliferative phase of the menstrual cycle and genes that are up or down regulated during the secretory phase of the menstrual cycle.

The specification demonstrates a working example of obtaining periurethral vaginal walls from women undergoing SUI as well as obtaining biopsies from control women undergoing benign gynecologic surgeries. The specification teaches that the samples were selected from subjects in proliferative and secretory phase of the menstrual cycle (see page 25, lines 35-37 and page 26, lines 1-10). The specification asserted that to verify genetic expression of pelvic ligamentous tissue is similar to periurethral vaginal tissue within the same individual, biopsies of the uterosacral ligament and periuerethral vaginal mucosa from size women was obtained and compared for TIMP-1 and estrogen receptor-alpha were almost the same for both types of tissues in all six women (see page

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21, lines 13-18). The specification demonstrated obtaining 11 stress urinary incontinent and 11 age matched continent women and only 10 samples met microarray quality criteria. The specification asserts that 90 candidate genes were identified as differentially expression with p values assessed as  $<.05$  and assert that 62 were up regulated and 28 were down regulated in periurethral vaginal tissue of SUI women in the proliferative phase and makes reference to table 2 (see page 21, lines 29-33). However, table 2 is missing from the specification and the specification does not disclose the data nor the sequences of the genes that were up or down regulated in periurethral vaginal tissue of SUI subjects. The specification does not provide any data associated with expression levels and SUI subjects. The specification does not indicate which genes are predictably correlative or how much expression and if an increase or decrease is predictably correlative to developing or having SUI.

The specification demonstrates a second working example of obtaining periurethral vaginal tissue obtained from 5 premenopausal women with SUI and 5 continent women that were in the secretory phase of the menstrual cycle. The specification asserts that 20 genes from SUI women were identified in vaginal wall tissue without statistical analysis and when changes were catalogued in four out of the five pairs of SUI subjects, 58 genes were unregulated and 36 were down regulated (see page 23, lines 24-30). However, the specification does not provide any data, statistically analysis, or nucleic acid sequences for the genes associated with SUI subjects. The specification lists genes that were upregulated or down regulated, however the specification does not provide which genes are predictably correlative to diagnosis of SUI.

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The specification asserts that figure 3 suggests that the analyzed genes may be important for distinguishing SUI and control pelvic supporting tissue phenotypes and may reflect complex genetic variations which may be predictive of the development of incontinence in individuals who have not yet developed the clinical symptoms of this conditions (see page 28, lines 12-15). Figure 3 lists genes, P values, and ave FC however it is unclear if the genes listed in figure 3 are for the study of patients in the secretory phase or proliferative phase of the menstrual cycle.

Although the specification asserts obtaining samples from different SUI subject and controls at the secretory and proliferative phase of the menstrual cycle in premenopausal women, the specification does not provide guidance for predictably correlating expression level of any gene and its comparison to a predetermined indicator gene to determine an individual that has or at risk of having SUI. The specification is merely prophetic that analysis of reproductive hormone-modulated gene expression in pelvic supporting tissue of a premenopausal subject and comparison of the results to a predetermined indicator is indicative of diagnosis and predisposition to stress urinary incontinence. For example, the specification does not teach the comparison of a gene expression study with a predetermined indicator, particularly a predetermined indicator that is evaluated prior to developing SUI. The specification does not teach any gene that can be used a predetermined indicator, particularly one that is determined at a time prior to appearance of symptoms of pelvic floor dysfunction. The specification does not teach a gene, including alpha 1 antitypsin that is predictably correlative to diagnosing or determining a predisposition to SUI in a subjection from obtaining a tissue during the

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secretory phase of the menstrual cycle. Furthermore, the specification does not teach gene expression analysis of tissue samples from vaginal cuff tissue, vaginal epithelium, and pelvic ligamentous tissue. The specification asserts an analysis of gene expression of proliferative phase subjects using periuterine tissue and an analysis of gene expression of secretory phase subjects using vaginal wall tissue. Furthermore, the specification does not provide any data for the analysis of alpha 1 antitrypsin and its association with SUI subjects. The specification asserts that measuring alpha 1 antitrypsin in pelvic supporting tissues of women with SUI and women at risk of developing SUI but does not provide guidance with respect to how much expression would predictably correlate with having or developing SUI. Does an increase or decrease in expression of alpha 1 antitrypsin of 1.0 indicate having or developing SUI? The specification is silent with regard to how much expression, for any gene, would be predictably correlative to determining a diagnosis or predisposition to SUI.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a gene expression levels is high, the level of unpredictability in associating any particular expression of a particular gene or combination of genes with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

While the claims of the instant application are broad and encompass analysis of any organism, the instant specification does not provides evidence of an association of any gene expression level, particularly, alpha 1 antityprsin that is correlated to SUI. It is

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unpredictable as to whether or not genes that are expressed in premenopausal subjects exists in any non-human organisms, and whether or not detection these genes in any other organism would be predictive of the having or developing SUI. For example, Mummididi et al. (2000). Mummididi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1<sup>st</sup> full paragraph). Thus it is entirely unpredictable as to whether or not gene expression of premenopausal subjects would be associated with SUI in any other non-human organism.

Furthermore, there is also a large amount of unpredictability with regard to comparing results from gene expression analysis data in human to other even closely related animals. Enard et al. (2002) teaches that large numbers of quantitative changes in gene expression can be detected between closely related mammals (p. 342, middle column, last paragraph).

Furthermore, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test that will yield statistically significant information to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Shalon et al. (US 2001/0051344 A1 Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon et al. further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and

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preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Sharlon et al. teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2<sup>nd</sup> column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1<sup>st</sup> column, 1<sup>st</sup> and 2<sup>nd</sup> full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2<sup>nd</sup> column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations

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wrong (see page 2, 1<sup>st</sup> paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3<sup>rd</sup> paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2<sup>nd</sup> paragraph). Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate the gene names from the gene library listed in the specification to specifically identify exposure, including length of exposure, to a specific toxic agent.

At the time of filing, the prior art teaches the unpredictability of associating gene expression levels with diagnosis of SUI. Applicant's own post filing art (Chen et al. Am J Obstet Gynecol, 2003, 189:89-97) teach a microarray analysis of genes associated with SUI subjects. Chen et al. teach that the microarray assay used in the study (similar to the assay used in the instant specification) lacks the necessary sensitivity to detect differences in expression levels of some mRNA genes that are present in low abundance (see page 96, 1<sup>st</sup> column, last paragraph). Chen et al. teach that defects in pelvic floor support take many decades to become evident which explains relatively small average fold change in gene expression and therefore the cutoff of 1.3 fold change was used (see pg. 96 last paragraph, 1<sup>st</sup> column con't to 2<sup>nd</sup> column, 1<sup>st</sup> paragraph). Chen et al. teach that this low fold change must be validated by other method and with a larger sample set (page 96, 2<sup>nd</sup> column, 1<sup>st</sup> paragraph). Chen et al. teach that the results are heterogeneity in expression and due to collagen metabolism in tissues throughout the pelvis, using tissue from the same individual as a continent control was not possible (see page 96, 2<sup>nd</sup> column, 1<sup>st</sup> full

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paragraph). Chen further teaches that most pelvic organ disorders results from a variety of causes and the difference between the SUI group and control may be different due to issues that are unrelated to connective tissue metabolism and future studies with larger sample sizes can help reduce these potential differences (see page 96, 2<sup>nd</sup> column, 1<sup>st</sup> full paragraph). Chen et al. teach the unpredictability of correlating the gene expression profile of 5 sample sets with diagnosis and predisposition to SUI as Chen teaches that the differences may be due to variety of causes.

Furthermore, an editorial comment to Chen et al. (Int. Urogynec. J. 2002, 13 :80-87) asserts that the paper highlights may difficulties of studying collagen metabolism in pelvic floor disorders and the researches struggled with the site of tissue sampling. The comment further asserts that it is premature to extrapolate any of the conjectures of this report to the afflicted patient population (see page 87, editorial comment).

Neither the art nor the specification teach gene expression and its comparison to a predetermined indicator gene that would be predictable to determine SUI or predisposition to SUI. It is unpredictable to detect alpha 1 antitrypsin in a premenopausal subject based on the teaching in the specification. The prior art supports the unpredictability of this area of technology.

#### Quantity of Experimentation

Given the lack of guidance in the specification with regard to which gene expression levels and predetermined indicator in any species would be acceptable to test for diagnosis of SUI or predisposition to SUI, along with the evidence in the art with regard to the gene expression studies, association of difficulties of analyzing pelvic floor disorders, coupled with the unpredictability to correlate gene studies, the quantity of

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experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies to determine if in fact there was either an association between the expression of any gene, specifically alpha 1 antitrypsin in premenopausal subjects with SUI and without SUI. The results of such a study are clearly unpredictable as evidence by lack of the teachings in the specification with regard to alpha 1 antitrypsin as a prognostic tool to detect SUI in both secretory and proliferative phase of premenopausal subjects, coupled with the teaching in the art that an expression levels of pelvic floor dysfunction are difficult to detect and differences may be due to different pelvic floor disorders. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine genes and predetermined indicator in each premenopausal subject in each species in each sample and then determine if these genes and predetermined indicator are predictably correlative to diagnosis of SUI. The skilled artisan would then have to screen variants to determine those that are associated with prognosis of any disease and disorder in all samples (tissues, cells, etc.) in all populations in all species. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to SUI. The skilled artisan would have to detect multiple types of pelvic supporting tissue in multiple different pelvic disorders. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

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***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1, 4-5, 7, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Falconer et al. (Maturitas 1996, 24 :197-204).

With regard to claim 1 4-5, 7, 9, Falconer et al. teach analysis of five different genes collagen, verisan, byglycan, and decorin and their expression levels in premenopausal and postmenopausal women by northern blot hybridization (claim 5 and 8) (see table 2). Falconer et al. teach analysis of biopsies taken transvaginally (claim 4).

It is noted that with respect to the novelty of the invention, the preamble is not given weight since the claim does not include a method step of correlating the gene expression level between the predetermined indicator and the reproductive hormone modulated gene expression with diagnosis of stress urinary incontinence. As such the claimed method only requires analysis of reproductive hormone modulated gene expression in pelvic supporting tissue and comparison to a predetermined indicator gene which is taught by Falconer et al. Falconer et al. teach analysis of mRNA expression of

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five genes between pre and postmenopausal women, which encompasses analysis of gene expression between a reproductive hormone modulating gene expression and a predetermined indicator.

15. Claims 1-2, 4-5, 7-9, are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (6<sup>th</sup> Int'l. Conf. On Extracellular Matric of Female Reproductive Tract, May 2001, abstract).

Chen et al. teach obtaining RNA from anterior vaginal cuff tissue (claim 4) from premenopausal women in the proliferative phase (claim 2) with and without urinary incontinence and hybridizing to HuGeneFl array (claim 5, 7-8). Chen et al. teach 133-upregulated gene and 263 down-regulated genes in the incontinent women compared to the continent women (claim 9).

It is noted that with respect to the novelty of the invention, the preamble is not given weight since the claim does not include a method step of correlating the gene expression level between the predetermined indicator and the reproductive hormone modulated gene expression with diagnosis of stress urinary incontinence. As such the claimed method only requires analysis of reproductive hormone modulated gene expression in pelvic supporting tissue and comparison to a predetermined indicator gene which is taught by Chen et al.

16. Claims 1, 4-7, and 9 rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Int. Urogynecol. J. 2002 13:80-87).

Chen et al. teach comparing gene expression of TIMP-1 mRNA expression in

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vaginal wall tissue (claim 4) of control group and patients with SUI (see figures 3-6).

Chen et al. teach mRNA expression analysis by competitive PCR (see page 82, 1<sup>st</sup> column, 2<sup>nd</sup> and 3<sup>rd</sup> paragraph) (claim 5-7).

It is noted that with respect to the novelty of the invention, the preamble is not given weight since the claim does not include a method step of correlating the gene expression level between the predetermined indicator and the reproductive hormone modulated gene expression with diagnosis of stress urinary incontinence. As such the claimed method only requires analysis of reproductive hormone modulated gene expression in pelvic supporting tissue and comparison to a predetermined indicator gene which is taught by Chen et al. Furthermore, Chen et al. teach the mean age of the incontinent group was 54-75 and the control group was 24-75, which encompasses premenopausal women.

17. Claims 1, 4-7, 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Polan et al. (US Patent 6420119, filed 10/11/2000)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Polan et al. teach identification of mRNA in vaginal tissue between incontinent and control women to measure the quantitative mRNA expression of MMP-1, 2, and 9 (see column 9, lines 26-43). Polan et al. teach isolation of vaginal cuff tissues from

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premenopausal women (claim 4) (see column 9, lines 60-65) and extraction of RNA (see column 10, lines 25-37). Polan et al. teach quantitative expression analysis by RT-PCR (see column 10, lines 38-62) (claims 5-7). Polan et al. teach gene expression ratios of MMP-2/TIMP-2 and MMP-1/TIMP-1 mRNA in control and SUI patients (see figure 2 and 3) (predetermined indicator is obtained during parallel measurements of SUI and controls) (claim 9).

It is noted that with respect to the novelty of the invention, the preamble is not given weight since the claim does not include a method step of correlating the gene expression level between the predetermined indicator and the reproductive hormone modulated gene expression with diagnosis of stress urinary incontinence. As such the claimed method only requires analysis of reproductive hormone modulated gene expression in pelvic supporting tissue and comparison to a predetermined indicator gene which is taught by Polan et al.

### ***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912.

The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

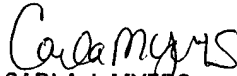
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PRIMARY EXAMINER

  
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Examiner  
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